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PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

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DATE: **July 17, 2002**

MEMORANDUM

SUBJECT: **CHLORSULFURON - Second** Report of the Hazard Identification Assessment Review Committee.

FROM: Linda L. Taylor, Ph.D.
Health Effects Division (7509C)

THROUGH: Elizabeth Doyle, Co-Chair
and
Jess Rowland, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Felicia Fort, Risk Assessor
Health Effects Division (7509C)

PC Code: 118601

On July 11, 2002, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) evaluated the 2-year chronic toxicity/3 generation reproduction combined study and reevaluated the chronic RfD and the long-term dermal and inhalation exposure risk assessments due to the fact that the previous study and endpoint selected was based on bensulfuron data. The conclusions drawn at this meeting are presented in this report.

Committee Members in Attendance

Members present were: Elizabeth Doyle (Co-Chair), Jess Rowland (Co-Chair), Steve Knizner, Elizabeth Mendez, David Nixon, John Liccione, Pamela Hurley, Brenda Tarplee

Member(s) in absentia: William Burnam, Ayaad Assaad

Data evaluation prepared by: Linda Taylor

Also in attendance were: Felicia Fort, Whang, Phang, Michael Metzger

Data Evaluation / Report Presentation

Linda L. Taylor, Ph.D.
Toxicologist

INTRODUCTION

The Health Effects Division's Hazard Identification Assessment Review Committee [HIARC] initially evaluated the toxicology database on chlorsulfuron on May 29, 2002. The HIARC reviewed the recommendations of the toxicology reviewer for Chlorsulfuron with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to chlorsulfuron was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996, in accordance with the OPP 10X guidance document. At this meeting, the HIARC reviewed the 2-year chronic toxicity/2-generation reproduction combined study in rats conducted with **ben**sulfuron. Based on the data on this chemical, the HIARC established the chronic RfD, conducted and FQPA assessment, and identified data gaps.

The purpose of the July 11, 2002 meeting was to evaluate the 2-year chronic toxicity/3-generation reproduction combined study in rats conducted with **chlorsulfuron,** correct the FQPA assessment, and revise the chronic RfD and chronic dermal and inhalation endpoints, which were erroneously based on bensulfuron studies previously.

I. FQPA HAZARD CONSIDERATIONS

1. Adequacy of the Toxicity Data Base

The HIARC concluded that the toxicology database for chlorsulfuron is not complete. Although the available 3-generation reproduction study on chlorsulfuron conformed to the old guideline requirements, it is unacceptable under the current guideline requirement in light of the fact that most of the parameters used for assessing susceptibility in infants and children are not provided in the available study. The studies available for FQPA considerations are:

- rat developmental toxicity study (acceptable)
- rabbit developmental toxicity study (acceptable)
- two-generation reproduction study in rats **(unacceptable, under current guidelines)**

2. Evidence of Neurotoxicity

The HIARC concluded that there is no concern for neurotoxicity. The acute neurotoxicity study and the subchronic neurotoxicity study are not required for chlorsulfuron.

3. Developmental Toxicity Study Conclusions

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 41983101), chlorsulfuron (98.2% a.i.; Lot# 12-51, Drum 14/Batch # 12-51-88) was administered to 20 artificially-inseminated female Hra: (NZW)SPF rabbits/dose once daily *via* gavage at dose levels of 0, 25, 75, 200, and 400 mg/kg/day [original study] and at 400 and 1000 mg/kg/day [supplemental study] from day 7 to 19

of gestation.

Maternal toxicity was evident at the 1000 mg/kg/day dose level, as evidenced by the death of 8 of the 20 does and 6 abortions. One doe in the 200 mg/kg/day dose group and one doe in one of the 400 mg/kg/day groups also aborted. Additionally, there was a negative body-weight gain during the initial 3 days of dosing at 200 mg/kg/day and 400 mg/kg/day in the original study and a substantial decrease in body-weight gain in the supplemental study at 400 and 1000 mg/kg/day. Adjusted maternal body-weight gain was substantially lower than control at the 200 [original study], 400 [original and supplemental studies], and 1000 mg/kg/day [supplemental study] dose levels [days 0-29: 78%, 54%, 43%, and 43% of control, respectively; days 7-29: 24% of control, -24 grams, -25 grams, -67 grams, respectively].

There were no treatment-related effects on pregnancy rate, numbers of corpora lutea/doe, implantations/doe, live fetuses/doe, resorptions/doe, or the sex ratio. In the supplementary study, there was an apparent treatment-related increase in the incidence of enlarged gallbladders [0, 2, 4 at 0, 400, and 1000 mg/kg/day, respectively] and mishappened gallbladders [0, 0, 2 at 0, 400, and 1000 mg/kg/day, respectively] .

The maternal toxicity LOAEL is 200 mg/kg/day, based on decreased body-weight gain. The maternal toxicity NOAEL is 75 mg/kg/day.

Developmental toxicity was observed at the 400 mg/kg/day dose level, as evidenced by the slight increase in the incidence of visceral malformations [absent gallbladder, doubled aorta, ventricular septal defect] compared to the control. Additionally, the female fetuses at the 400 mg/kg/day dose level displayed a slightly lower body weight [90% of control] compared to the control, and the mean litter weight at this dose level was slightly decreased [≈90% of control]. The 1000 mg/kg/day dose level resulted in severe maternal toxicity and therefore, the developmental findings at this dose level [lack of effect] are not considered reliable.

The developmental toxicity LOAEL is 400 mg/kg/day, based on a slight increase in visceral malformations and decreased fetal body weight. The developmental toxicity NOAEL is 200 mg/kg/day.

The developmental toxicity study in the rabbit is classified Acceptable/Guideline, and it satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3*(b)*) in rabbits.

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 41976406), chlorsulfuron (98.2%, Lot 12-51, drum 14; batch 12-51-88) was administered by gavage to Crl:CD®Br rats from gestation days 7-16. Dose groups were 0, 55, 165, 500, or 1500 mg/kg/day and there were 25 presumed pregnant rats per group.

Dams in the 500 mg/kg/day group had clinical signs (vaginal discharge with associated alopecia). There were two treatment-related maternal deaths in the 1500 mg/kg/day group. Dams in the 1500 mg/kg/day group had more clinical signs (swollen limbs and faces), and decreased corrected body weight gain which was accompanied by decreased food consumption. **The maternal NOAEL is 165 mg/kg/day based upon clinical signs (vaginal discharge with associated alopecia) at the**

maternal LOAEL of 500 mg/kg/day.

Fetal toxicity was limited to decreased fetal weight in the 1500 mg/kg/day group. There were no teratogenic effects. **The developmental NOAEL is 500 mg/kg/day based upon decreased fetal weight at the developmental LOAEL of 1500 mg/kg/day.**

This study is classified **acceptable/guideline** and **satisfies** requirements for a developmental toxicity study in rats (OPPTS 870.3700; OECD 414).

4. Reproductive Toxicity Study Conclusions

EXECUTIVE SUMMARY: No new review was performed on this study, and an EXECUTIVE SUMMARY was not generated. In a three-generation reproduction study (MRID 00086003), chlorsulfuron technical (95% a.i.) was administered to CD® in the diet at dose levels of 0, 100, 500, and 2500 ppm (standard conversion factor used: 0, 5, 25, and 125 mg/kg/day). Two litters were produced per generation.

No compound-related signs of parental toxicity were noted at any dose level. The only effect reported was slightly decreased fertility indices at the high-dose level compared to the control. The mean number of pups/litter, gestation lactation, and viability indices, litter survival, mean weanling body weights and body-weight gains, diet consumption and food efficiency were not adversely affected in any generation. There were no treatment- or dose-related clinical observations, and weanling organ weights were comparable among the groups. No gross or histopathological abnormalities were observed in the F3b weanlings.

The reproductive NOEL is 100 ppm (5 mg/kg/day), and the reproductive LOEL is 500 ppm (25 mg/kg bw/day), based on decreased fertility.

This study is **unacceptable/non-guideline** and it does not satisfy the guideline requirement for a two-generation reproductive study (OPPTS 870.3800; OECD 416) in rats. This study had numerous deficiencies including but not limited to: 1) no assessment of estrous cyclicity, sperm parameters, 2) no assessment of male reproductive performance, 3) parental animals not subjected to gross pathology or histopathology examinations, 4) no assessment of developmental landmarks, and 5) pup histopathology evaluations conducted only for the F3B generation. Although this reproduction study on chlorsulfuron conformed to the old guideline requirements, it is unacceptable under the current guideline requirement in light of the fact that most of the parameters used for assessing susceptibility are not provided in the available study

5. Additional Information from Literature Sources

No other information was located in the literature for chlorsulfuron.

6. Pre-and/or Postnatal Toxicity

The HIARC concluded that there is not a concern for pre- and/or postnatal toxicity resulting from exposure to chlorsulfuron.

A. Determination of Susceptibility: There is no evidence of increased susceptibility [qualitative and quantitative] following *in utero* exposure to chlorsulfuron in either the rat or rabbit developmental toxicity study. The HIARC concluded that susceptibility cannot be assessed in the 2-generation reproduction study in rats.

B. Degree of Concern Analysis and Residual Uncertainties: Susceptibility could not be determined in the 3-generation reproduction study because it did not meet the current guideline requirements in light of the fact that most of the parameters used for assessing susceptibility were not available (the study was conducted in 1978). Although susceptibility could not be assessed, there is confidence in the results of the study. It was determined that there is low level of concern and no residual uncertainties for the effects (decreased fertility in F3 generation) seen because there was no decrease in fertility in either the F1 or F2 generations, and the decrease in fertility seen in the F3 generation was minimal and of questionable toxicological significance at the highest dose tested (125 mg/kg/day). Based on the minimal effects, a conservative NOEL of 25 mg/kg/day was established; review of the fertility data indicate that the next highest dose of 125 mg/kg/day could be the NOAEL. The HIARC determined that a 2-generation reproduction study that meets the current standards is required to meet the FQPA requirements.

In accordance with the 2002 OPP 10X Guidance Document, the HIARC determined that a Database Uncertainty Factor of 3X is required for the lack of an acceptable 2-generation reproduction study in rats. An UF of 3X (as opposed to a 10X) is adequate because the chronic RfD is based on the NOEL of 5 mg/kg/day, which is 5X lower than the conservative NOAEL of 25 mg/kg/day established and could be 25X lower if the NOAEL is established at 125 mg/kg/day in the existing 3-generation reproduction study (as discussed above).

C. Proposed Hazard-based Special FQPA Safety Factor(s): The HIARC concluded that the hazard-based special FQPA safety factor could be removed [1X], since any residual concern is addressed by the database uncertainty factor.

7. Recommendation for a Developmental Neurotoxicity Study

The HIARC concluded that there is no concern for developmental neurotoxicity resulting from exposure to chlorsulfuron. A developmental neurotoxicity study [DNT] in rats is not required.

A. Evidence that suggest requiring a Developmental Neurotoxicity study:
None.

B. Evidence that do not support a need for a Developmental Neurotoxicity study:

- Lack of evidence of neurotoxicity in the available database on chlorsulfuron.
- Lack of evidence for pre-natal toxicity

II. HAZARD IDENTIFICATION

1. Acute Reference Dose (aRfD) - General Population

An appropriate end point to quantify a single-dose exposure was not available in the database.

2. Acute Reference Dose (aRfD) - Females 13-50

An appropriate end point to quantify a single-dose exposure was not available in the database.

3. Chronic Reference Dose (cRfD)

Study Selected: chronic toxicity/carcinogenicity study - rat OPPTS 870.4300; §83-5

MRID No.: 00086003

Executive Summary: In a chronic toxicity study (MRID 00086003), chlorsulfuron technical (95%) was administered to CD® rats (80/sex/dose) in the diet at dose levels of 0, 100, 500, and 2500 ppm (standard conversion factor used: 0, 5, 25, 125 mg/kg body weight/day for 2 years. At the 1 year interim sacrifice 10 rats/sex/dose were sacrificed and subjected to a gross necropsy and histopathological evaluation.

A statistically significant decrease in body weight was reported in males at the mid- (4%-5% decrease) and high-dose levels (4%-9% decrease) at various time during the study. Body-weight gains were decreased in these groups also (5%-10% decrease). Body weights and body-weight gains were comparable among the female groups. Food consumption was comparable among the groups for both sexes, but food efficiency was decreased for the males at the high-dose level. Clinical signs, palpable tissue masses, and mortality were comparable among the groups for both sexes. No treatment-related findings were observed in the hematology and clinical chemistry parameters monitored for either sex. There were no adverse effects on organ weights in either sex. There were no treatment-related gross or histopathological abnormalities observed in either sex at any dose level, and there was no increase in the incidence of any tumor. Although the high-dose males [13/69] displayed a higher incidence of unilateral interstitial cell tumors compared to the control [2/68], this was not considered treatment-related since a compound-induced effect would be expected to affect the testes bilaterally. The incidence of bilateral interstitial cell tumors in male rats in the control group [7/68] was greater than the incidence at the high dose [3/69]. Additionally, the unilateral incidence was within the known spontaneous range for CD® rats, and there were no other changes [e.g., interstitial cell hyperplasia] suggestive of a compound-related tumorigenic effect in the testes.

Under the conditions of this study, the NOEL is 100 ppm (5 mg/kg/day). The LOEL is 500 ppm (25 mg/kg/day) based on decreased body weight in males.

At the doses tested, there was not a treatment related increase in tumor incidence when compared to controls. Dosing was considered adequate based on decreases in body weight and food efficiency at the highest dose tested.

This chronic toxicity/carcinogenicity study in the rat is **acceptable/guideline,** and it satisfies the general guideline requirement for a chronic toxicity/carcinogenicity study OPPTS 870.4300);OECD 453] in rats.

Dose and Endpoint for Establishing cRfD: **NOEL = 5 mg/kg/day**, based on decreased body weight at the LOEL of 25 mg/kg/day.

Uncertainty Factor(s): 300X [10 interspecies; 10X intraspecies; 3X database uncertainty factor]

Comments about Study/Endpoint/Uncertainty Factor: The route and duration of exposure are appropriate for selection of the chronic dietary endpoint. An additional 3X database uncertainty factor is required for the incomplete database [lack of a 2-generation reproduction study].

$$\textbf{Chronic RfD} = \frac{5 \text{ mg/kg/day}}{300} = \textbf{0.02 mg/kg/day}$$

4. Incidental Oral Exposure: Short-Term (1-30 days)

Study Selected: developmental toxicity - rabbit OPPTS 870.3700; §83-3 (b)

MRID No.: 41983101

Executive Summary: Executive Summary: In a developmental toxicity study (MRID 41983101), chlorsulfuron (98.2% a.i.; Lot# 12-51, Drum 14/Batch # 12-51-88) was administered to 20 artificially-inseminated female Hra: (NZW)SPF rabbits/dose once daily *via* gavage at dose levels of 0, 25, 75, 200, and 400 mg/kg/day [original study] and at 400 and 1000 mg/kg/day [supplemental study] from day 7 to 19 of gestation.

Maternal toxicity was evident at the 1000 mg/kg/day dose level, as evidenced by the death of 8 of the 20 does and 6 abortions. One doe in the 200 mg/kg/day dose group and one doe in one of the 400 mg/kg/day groups also aborted. Additionally, there was a negative body-weight gain during the initial 3 days of dosing at 200 mg/kg/day and 400 mg/kg/day in the original study and a substantial decrease in body-weight gain in the supplemental study at 400 and 1000 mg/kg/day. Adjusted maternal body-weight gain was substantially lower than control at the 200 [original study], 400 [original and supplemental studies], and 1000 mg/kg/day [supplemental study] dose levels [days 0-29: 78%, 54%, 43%, and 43% of control, respectively; days 7-29: 24% of control, -24 grams, -25 grams, -67 grams, respectively].

There were no treatment-related effects on pregnancy rate, numbers of corpora lutea/doe, implantations/doe, live fetuses/doe, resorptions/doe, or the sex ratio. In the supplementary study,

there was an apparent treatment-related increase in the incidence of enlarged gallbladders [0, 2, 4 at 0, 400, and 1000 mg/kg/day, respectively] and misshapened gallbladders [0, 0, 2 at 0, 400, and 1000 mg/kg/day, respectively] .

The maternal toxicity LOAEL is 200 mg/kg/day, based on decreased body-weight gain. The maternal toxicity NOAEL is 75 mg/kg/day.

There was a slight increase in the incidence of visceral malformations [absent gallbladder, doubled aorta, ventricular septal defect; one fetus/malformation; 3 litters] compared to the control at the 400 mg/kg/day dose level, but this was not considered an effect of treatment. Developmental toxicity was observed at the 400 mg/kg/day dose level, as evidenced by the slightly lower fetal body weight [90% of control] in the females compared to the control females, and the slightly decreased [≈90% of control] mean litter weight. The 1000 mg/kg/day dose level resulted in severe maternal toxicity and therefore, the developmental findings at this dose level [lack of effect] are not considered reliable.

The developmental toxicity LOAEL is 400 mg/kg/day, based on decreased fetal body weight. The developmental toxicity NOAEL is 200 mg/kg/day.

The developmental toxicity study in the rabbit is classified Acceptable/Guideline, and it satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3*(b)*) in rabbits.

Dose and Endpoint for Risk Assessment: **Maternal toxicity NOAEL = 75 mg/kg/day**, based on decreased body weight/body-weight gain in females at 200 mg/kg/day.

Comments about Study/Endpoint: Although the dog 6-month study provides a lower NOAEL [18.5 mg/kg/day], due to the fact that the dogs at study initiation were between 9 and 11 months old, an assessment of the young, growing, animal was not performed. Also, body weights in older [not growing] dogs are variable, and there is little confidence in the effect level. Additionally, in the chronic dog study in which the dogs were 6.5 months old at study initiation, decreased body-weight gain [91% of control] for the 0-13 week interval was observed in females at 215 mg/kg/day [NOAEL of 60.6 mg/kg/day].

5. Incidental Oral Exposure: Intermediate-Term (1 - 6 Months)

Study Selected: developmental toxicity study - rabbit OPPTS 870.3700/§83-3 (b)

MRID No.: 41983101

Executive Summary: See under Short-Term Incidental Oral Exposure.

Dose and Endpoint for Risk Assessment: **Maternal toxicity NOAEL = 75 mg/kg/day**, based on decreased body weight/body-weight gain in females at 200 mg/kg/day

Comments about Study/Endpoint: See under Short-Term Incidental Oral Exposure.

6. Dermal Absorption

Dermal Absorption Factor: 100% (default value), based on the lack of a dermal absorption study.

7. Dermal Exposure: Short-Term (1- 30 days) Exposure

Study Selected: developmental toxicity study - rabbit OPPTS 870.3700/§83-3 (b)

MRID No.: 41983101

Executive Summary: See under Short-Term Incidental Oral Exposure.

Dose and Endpoint for Risk Assessment: **Maternal toxicity NOAEL = 75 mg/kg/day**, based on decreased body weight/body-weight gain in females at 200 mg/kg/day

Comments about Study/Endpoint: See under Short-Term Incidental Oral Exposure. Since no dermal absorption data are available, toxicity by the dermal route will be considered to be equivalent to toxicity by the oral route of exposure.

8. Dermal Exposure: Intermediate-Term (1 - 6 Months)

Study Selected: developmental toxicity study - rabbit OPPTS 870.3700/§83-3 (b)

MRID No.: 41983101

Executive Summary: See under Short-Term Incidental Oral Exposure.

Dose and Endpoint for Risk Assessment: **Maternal toxicity NOAEL = 75 mg/kg/day**, based on decreased body weight/body-weight gain in females at 200 mg/kg/day

Comments about Study/Endpoint: See under Short-Term Incidental Oral Exposure. Since no dermal absorption data are available, toxicity by the dermal route will be considered to be equivalent to toxicity by the oral route of exposure.

9. Dermal Exposure Long-Term (> 6 Months)

Study Selected: chronic toxicity/carcinogenicity study - rat OPPTS 870.4300/§83-5

MRID No.: 00086003

Executive Summary: See under Chronic RfD.

Dose and Endpoint for Risk Assessment: **NOEL = 5 mg/kg/day**, based on decreased body weight at the LOEL of 25 mg/kg/day.

Comments about Study/Endpoint: See under Chronic RfD. The selected study is an oral study. Since no dermal absorption data are available, toxicity by the dermal route will be considered to be equivalent to toxicity by the oral route of exposure.

10. Inhalation Exposure: Short -Term (1- 30 days)

Study Selected: developmental toxicity study - rabbit OPPTS 870.3700/§83-3 (b)

MRID No.: 41983101

Executive Summary: See under Short-Term Incidental Oral Exposure.

Dose/Endpoint for Risk Assessment: **Maternal toxicity NOAEL = 75 mg/kg/day**, based on decreased body weight/body-weight gain in females at 200 mg/kg/day

Comments about Study/Endpoint: See under Short-Term Incidental Oral Exposure. Since no inhalation absorption data are available, toxicity by the inhalation route will be considered to be equivalent to toxicity by the oral route of exposure.

11. Inhalation Exposure: Intermediate-Term (1- 6Months)

Study Selected: developmental toxicity study - rabbit OPPTS 870.3700/§83-3 (b)

MRID No.: 41983101

Executive Summary: See under Short-Term Incidental Oral Exposure.

Dose/Endpoint for Risk Assessment: **Maternal toxicity NOAEL = 75 mg/kg/day**, based on decreased body weight/body-weight gain in females at 200 mg/kg/day

Comments about Study/Endpoint: See under Short-Term Incidental Oral Exposure. Since no inhalation absorption data are available, toxicity by the inhalation route will be considered to be equivalent to toxicity by the oral route of exposure.

12. Inhalation Exposure: Long-Term (> 6 Months)

Study Selected: chronic toxicity/carcinogenicity study - rat OPPTS 870.4300/§83-5

MRID No.: 00086003

Executive Summary: See under Chronic RfD.

Dose and Endpoint for Risk Assessment: **NOEL = 5 mg/kg/day**, based on decreased body weight at the LOEL of 25 mg/kg/day.

Comments about Study/Endpoint: See under Chronic RfD. Since no inhalation absorption data are available, toxicity by the inhalation route will be considered to be equivalent to toxicity by the oral route of exposure.

13. Margins of Exposure

The target Margins of Exposure (MOEs) for **occupational** exposure risk assessments are as follows:

Route / Duration	Short-Term (1-30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Dermal	100	100	100
Inhalation	100	100	100

The target MOEs for **residential** exposure risk assessments will be determined by the FQPA Safety Factor Committee and should include the database uncertainty factor of 3X for lack of an adequate 2-generation reproduction study.

14. Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. The toxicity endpoints selected for these routes of exposure may be aggregated as follows: for short-, intermediate- and long-term aggregate exposure risk assessments, the oral, dermal and inhalation routes can be combined because of the common toxicity endpoint (decreased body weight/body weight gain) via these routes.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No. 00086003

Executive Summary: See under Chronic RfD.

Discussion of Tumor Data There was no treatment-related increase in tumor incidence in either sex.

Adequacy of the Dose Levels Tested: A statistically significant decrease in body weight was reported in males at the mid- (4%-5% decrease) and high-dose levels (4%-9% decrease) at various time during the study. Body-weight gains were decreased in these groups also (5%-10% decrease). Body weights and body-weight gains were comparable among the female groups

2. Carcinogenicity Study in Mice

MRID No. 00090030

Executive Summary: In a carcinogenicity study (MRID 00090030) INW-4189 (91.9-95% a.i., Lots INW-4189-22 and INW-4189-57) was administered to 80 CD-1 mice/sex/dose in the diet at dose levels of 0, 100, 500 or 5000 ppm (**approximately 0, 15, 108 and 750 mg/kg bw/day based on 1 ppm in food equals 0.15 mg/kg/day**) for 104 weeks.

There were no treatment-related effects on survival, clinical observations, hematology or post-mortem examinations. Food consumption measurements were complicated by spillage. Body weight was statistically significantly decreased relative to control values for the 5000 ppm males and females during most of the study. However, the effect was marginal with decreases of mostly less than 10%. Body weight gain in the 5000 ppm males was significantly decreased at many time periods during the study (decreases for weeks 0-13, 0-26, 0-52 and 0-104 were 5%, 13%, 9% and 8%, respectively). Sporadic significant decreases were also observed in the 100 and 500 ppm males. Body weight gain was significantly decreased in the 5000 ppm females at many time periods (decreases for weeks 0-26, 0-52 and 0-104 were 13%, 16% and 9%, respectively). There were also decreases in the 500 ppm females at weeks 0-26 (10%) and 0-52 (9%). For weeks 0-52, there was a significant decrease (7%) in the 100 ppm females. Only the body weight gain decreases in the 5000 ppm males and females are considered toxicologically significant as they occurred consistently throughout the study, whereas the effects in the 100 and 500 ppm groups were sporadic.

The LOAEL is 5000 ppm (750 mg/kg/day) based on decreased body weight and body weight gain. The NOAEL is 500 ppm (108 mg/kg/day).

At the doses tested, there was no treatment related increase in tumor incidence when compared to controls. The decreases in body weight and body weight gain were marginal evidence of toxicity; therefore, the dosing is considered adequate.

This carcinogenicity study is **acceptable (guideline)** and **satisfies** the guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in mice.

Discussion of Tumor Data: There were no treatment-related increases in tumor incidence in either sex.

Adequacy of the Dose Levels Tested: In the subchronic mouse study, the dose levels were 500, 2500, 5000, and 7500 ppm [equivalent to 150, 783, 1557, and 2130 mg/kg/day in males; and 220, 1214, 2134, 3176 mg/kg/day in females]. Both sexes displayed sporadic decreases in body-weight gain and food efficiency during the study, which at times were substantial, but a dose response was not evident. The NOAEL was set at 5000 ppm [males 1557/females 2134 mg/kg/day], based on an increased incidence of retinal dysplasia and adrenal capsular cell proliferation. The high dose in the carcinogenicity study was 5000 ppm; however, due to the fact that the food consumption values are inflated, the calculation of the dose on a mg/kg/day basis is flawed and the standard conversion of

1 ppm = 0.15 mg/kg/day is appropriate. The dose levels are considered adequate for the assessment of carcinogenic potential, based on the marginal decreases in body weight/body-weight gain observed throughout most of the study at 5000 ppm [750 mg/kg/day].

Classification of Carcinogenic Potential: The HED RfD Peer Review Committee concluded that there was no evidence of carcinogenicity in rats or mice [TXR # 004995, dated 3/12/86].

IV. MUTAGENICITY

The HIARC concluded that there is not a concern for mutagenicity resulting from exposure to chlorsulfuron.

V. HAZARD CHARACTERIZATION

Chlorsulfuron is not acutely toxic *via* the oral and inhalation [Toxicity Category IV] routes of exposure and *via* the dermal [Toxicity Category III] route of exposure.

Adequate data are not available for an assessment of eye or skin irritation potential or for dermal sensitization potential.

A 21-day repeat dose dermal study and a subchronic inhalation study are not available on chlorsulfuron.

The chronic data provide no evidence that chlorsulfuron is particularly toxic to any organ or tissue.

Developmental toxicity was observed in both the rat and rabbit, as evidenced by decreased fetal body weights in both species. Maternal toxicity was observed as decreased body-weight gain in the rabbit and as an increased incidence of clinical signs [vaginal discharge with alopecia] in the rat.

Although unacceptable, reproductive toxicity was observed in the rat 3-generation reproduction study, as evidenced by decreased fertility of the dams in the F3 generation. No parental or offspring toxicity was observed, but there are several deficiencies [male reproductive performance not evaluated; parental animals not subjected to gross pathology or histopathology examinations; only F3b generation was examined; developmental landmarks not evaluated; estrous cyclicity, sperm parameters no evaluated], and the study is considered Unacceptable.

The data provided no indication of increased susceptibility of rats or rabbits to in utero exposure to chlorsulfuron. Due to multiple deficiencies, the data from the available 3-generation reproduction study on chlorsulfuron are not interpretable with respect to whether chlorsulfuron results in increased susceptibility following in utero and/or early postnatal exposure. The HED HIARC determined that a 2-generation reproduction study is required. Additionally, the HIARC determined that based on the lack of evidence for neurotoxicity, an acute neurotoxicity study, a subchronic neurotoxicity study, and a developmental neurotoxicity study are not required for chlorsulfuron.

No effects were observed on the endocrine system in any of the available studies on chlorsulfuron.

There is no evidence of carcinogenicity in rats or mice following oral exposure to chlorsulfuron. The mutagenic data indicate that there is no concern for mutagenicity.

Chlorsulfuron is rapidly absorbed, metabolized, and excreted in rats. There are no remarkable sex-, dose- or treatment-regiment-related differences in the absorption, distribution, and excretion of chlorsulfuron in rats. The major routes of elimination are *via* the urine (58-72% of the dose) and feces (20-35%). Negligible amounts (<0.08%) of radioactivity are found in the expired air as carbon dioxide. Small amounts of radioactivity were found in the tissues 3 days after dosing, with the highest concentrations being observed in the liver and whole blood in both sexes.

There are data gaps: (1) 2-generation reproduction study in the rat; (2) 21-day repeated dose dermal toxicity study; (3) subchronic inhalation study in the rat.

VI. **DATA GAPS / REQUIREMENTS** The following are datagaps for chlorsulfuron: 2-generation reproduction study, 21-day repeat dermal toxicity study, subchronic inhalation study.

VII. ACUTE TOXICITY

Acute Toxicity of Chlorsulfuron

Guideline No.	Study Type	MRID #(s)	Results	Toxicity Category
81-1	Acute Oral	00031406	LD_{50} = 5.5/6.3 g/kg♪	IV
81-2	Acute Dermal	00083956	LD_{50} = 3400 mg/kg	III
81-3	Acute Inhalation	00086825	LC_{50} = 5.9 m/L	IV
81-4	Primary Eye Irritation	00031414√	not an eye irritant	IV
81-5	Primary Skin Irritation	00031417√	no adequate study	-
81-6	Dermal Sensitization	00031417√	no adequate study	-

♪ males/females; √ classified unacceptable/nonguideline

VIII. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

Summary of Toxicology Endpoint Selection for Chlorsulfuron

Exposure Scenario	Dose (mg/kg/day) UF /MOE	Hazard Based Special FQPA Safety Factor	Endpoint for Risk Assessment
Dietary Risk Assessments			
Acute Dietary females 13-50 years of age	**no appropriate endpoint/dose identified**		
Acute Dietary general population including infants and children	**no appropriate endpoint/dose identified**		
Chronic Dietary all populations	NOAEL= **5 mg/kg/day** UF = **[300]** **Chronic RfD** = **0.02** mg/kg/day	1X	**rat chronic toxicity/carcinogenicity** LOAEL = **25 mg/kg/day** based on **decreased body weight in males**
Incidental Oral Short-Term (1 - 30 Days) Residential Only	NOAEL= **75 mg/kg/day** **MOE**= TBD	1X	**rabbit developmental toxicity** LOAEL = **200** mg/kg/day based on **decreased body-weight gain.**
Incidental Oral Intermediate-Term (1 - 6 Months) Residential Only	NOAEL= **75 mg/kg/day** **MOE** = TBD	1X	**rabbit developmental toxicity** LOAEL = **200** mg/kg/day based on **decreased body-weight gain.**
Non-Dietary Risk Assessments			
Dermal [a] Short-Term (1 - 30 days)	**Oral** NOAEL= 75 mg/kg/day	1X	**rabbit developmental toxicity** LOAEL = **200** mg/kg/day based on **decreased body-weight gain.**
Residential	**MOE** = TBD	1X	
Occupational	**MOE** = 100	1X	

Exposure Scenario	Dose (mg/kg/day) UF /MOE	Hazard Based Special FQPA Safety Factor	Endpoint for Risk Assessment
Dermal [a] Intermediate-Term (1 - 6 Months)	**Oral** NOAEL= 75 mg/kg/day		**rabbit developmental toxicity** LOAEL = **200** mg/kg/day based on **decreased body-weight gain.**
Residential	**MOE** = TBD	1X	
Occupational	**MOE** = 100	1X	
Dermal [a] Long-Term (> 6 Months)	**Oral** NOAEL= 5 mg/kg/day		**rat chronic toxicity/carcinogenicity** LOAEL = **25** mg/kg/day based on **decreased body-weight gain.**
Residential	**MOE** = TBD	1X	
Occupational	**MOE** = 100	1X	
Inhalation [b] Short-Term (1 - 30 days)	**Oral** NOAEL= 75 mg/kg/day		**rabbit developmental toxicity** LOAEL = **200** mg/kg/day based on **decreased body-weight gain.**
Residential	**MOE** = TBD	1X	
Occupational	**MOE** = 100	1X	
Inhalation [b] Intermediate-Term (1 - 6 Months)	**Oral** NOAEL= 75 mg/kg/day		**rabbit developmental toxicity** LOAEL = **200** mg/kg/day based on **decreased body-weight gain.**
Residential	**MOE** = TBD	1X	
Occupational	**MOE** = 100	1X	
Inhalation [b] Long-Term (>6 Months)	**Oral** NOAEL= 5 mg/kg/day		**rat chronic toxicity/carcinogenicity** LOAEL = **25** mg/kg/day based on **decreased body-weight gain.**
Residential	**MOE** = TBD	1X	
Occupational	**MOE** = 100	1X	
Cancer	**Classification:** no evidence of carcinogenicity		

a Since an oral NOAEL/LOAEL was selected, absorption *via* the dermal route is assumed to be equivalent to oral absorption.
b Since an oral NOAEL/LOAEL was selected, absorption *via* inhalation is assumed to be equivalent to oral absorption.
TBD = To Be Determined. Target MOEs for residential exposures will be determined by the FQPA Safety Factor Committee, and should include the database uncertainty factor of 3X for lack of an adequate 2-generation reproduction study.

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